REMARKS

Claims 19-21, 24, 26-37, 39, and 41 are pending. Claims 19-21, 24, 26-32, 34-37, and 39 have been amended without prejudice or disclaimer as to the underling subject matter. Claims 22-23, 25, 38, and 40 have been canceled without prejudice or disclaimer as to the underlying subject matter. Claim 41 has been newly added. Support for the foregoing amendment can be found throughout the specification and claims as originally filed, for example, at page 8, lines 7-22; page 11, lines 1-20; page 12, lines 6-13; page 13, lines 15-29; page 14, lines 2-6; and Figures 1, 4, and 34. No new matter enters by way of the foregoing amendment.

I. Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 19-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way so as to enable those skilled in the art to make and/or use the invention commensurate in scope with the claims. Office Action at page 2.

Applicants respectfully disagree with the Examiner's rejections under 35 U.S.C. § 112, first paragraph, enablement. However, solely in order to facilitate prosecution, Applicants have amended the claims without prejudice or disclaimer. As such, Applicants respectfully assert that the claim rejections are rendered moot.

At the outset, Applicants thank the Examiner for acknowledging that the specification is enabled for "the fusion polypeptide of SEQ ID NO: 3, nucleic acid encoding SEQ ID NO: 3, vectors and host cells containing this sequence, and methods of treatment by administering the fusion polypeptide of SEQ ID NO:3." *Id.* Applicants also thank the Examiner for indicating that the specification discloses the production of numerous other fusion proteins, such as SEQ ID NOs: 4-8. *Id.* at page 3. Indeed, the specification is enabled for peptides, vectors, host cells, and methods of using SEQ ID NO: 3, as well as for numerous additional fusion polypeptides. Moreover, the specification provides evidence that numerous fusion polypeptides, including those which contain the structural "RGD" or "NGR" amino acid motif, are capable of binding to $\alpha_v\beta_3$ on endothelial cells. Specification, for example, at Figure 1 and Example 3. Given this, one

of ordinary skill in the art would have the ability to practice the claimed invention with no undue experimentation.

The Office has not met the evidentiary burden to impose an enablement rejection. A specification that discloses how to use a claimed invention "must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995), *quoting In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) (emphasis in original). In rejecting the claims, the Office has not met this burden.

While Applicants agree with the Examiner's acknowledgement that the fusion polypeptide of SEQ ID NO: 3 satisfies the enablement requirement, Applicants disagree with the Examiner's assertion that none of the other claimed fusion polypeptides satisfy the enablement requirement. Office Action at page 4. Specifically, Applicants disagree with the Examiner's assertion that the specification does not demonstrate that SEQ ID NOs: 4-8 have the ability to selectively bind to tumor vessel endothelial cells. *Id.* Applicants further disagree with the Examiner's assertion that "[o]nly the fusion peptide of SEQ ID NO: 3 contains the RGD sequence disclosed as being specific for $\alpha_v\beta_3$-integrin." *Id.* The Examiner has not provided any reason to doubt the objective truth of the statements contained in the specification.

In addition to the specification, evidence that the claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, can be found in Kessler *et al.* (*Current Drug Discovery Technologies*, 2008, Vol. 5, pages 1-8). Kessler *et al.* is co-authored by Wolfgang E. Berdel and Rolf M. Mesters, both inventors of the current application. Without being limited, Kessler *et al.* provides evidence that numerous fusion polypeptides containing the "RGD" or "NGR" amino acid motif selectively bind to tumor vessel endothelial cells and retain high coagulatory activity. For example, Table 1 and Figure 3 of Kessler *et al.* indicate that numerous fusion peptides comprising the structural motif "NGR," such as tTF-cNGR1 (SEQ ID NO: 6), tTF-cNGR2 (SEQ ID NO: 7)and tTF-cNGR3 (SEQ ID NO: 8), selectively bind to tumor vessel endothelial cells and retain high coagulatory activity. Kessler *et al.* at page 2 and at Table 1 and Figure 3. Further, Kessler *et al.* provides sufficient evidence that fusion polypeptides comprising the structural motif "RGD" also selectively bind to tumor vessel endothelial cells and

retain high coagulatory activity. *Id.* at Table 1 and Figure 3. As such, one of skill in the art would have the ability to practice the invention in a manner which is commensurate in scope with the claims without undue experimentation.

Applicants further disagree with the Examiner's assertion that the claims should be limited to methods of treating human malignant melanoma, human fibrosarcoma, lung carcinoma, sarcoma, and carcinoma with the fusion polypeptide of SEQ ID NO: 3. Office Action at page 5. As described above, Kessler *et al.* provides evidence that a broad range of fusion polypeptides containing the "RGD" or "NGR" structural amino acid motif selectively bind to tumor vessel endothelial cells and retain high coagulatory activity. Kessler *et al.* also provides evidence that fusion peptides of the invention have the ability to reduce breast tumors and treat melanoma. Kessler *et al.* at page 5, column 2 - page 6, column 1, Figure 5, and Figure 7. With this, one of skill in the art would have the ability, without undergoing undue experimentation, to use fusion polypeptides of the invention to treat both breast tumors and melanoma.

Moreover, Bieker *et al.*, an unpublished article currently going through the peer-review process co-authored by Wolfgang E. Berdel and Rolf M. Mesters, provides further evidence that fusion peptides of the invention are capable of treating adenocarcinoma, melanoma, and fibrosarcoma. *See* Bieker *et al.*, "Infarction of tumor vessels by NGR-peptide directed targeting of tissue factor. Experimental results and first-in-man experience," unpublished manuscript. For example, Bieker *et al.* indicates that fusion polypeptides including tTF coupled with a NGR-based peptide, GNGRAHA (SEQ ID: NO: 4), selectively binds to tumor vessel endothelial cells. Results obtained with NGR-based peptides in animals indicate that polypeptides comprising tTF coupled to a NGR amino acid motif have the ability to induce tumor growth retardation and regression in adenocarcinoma, melanoma, and fibrosarcoma. Specifically, Bieker *et al.* provides evidence that fusion polypeptides of the invention can effectively treat human patients with adenocarcinoma, cholangiocarcinoma, malignant ascites, mesothelioma, multiple myeloma with extramedullar tumor formation, metastatic germ cell tumor. Bieker *et al.* at pages 17-18 and Figure 9.

Applicants have sufficiently described the claimed invention such that one of skill in the art in light of the specification would be able to practice the invention commensurate in scope

with the claims. In sum, such disclosure provides adequate direction, including working examples, to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

Accordingly, for at least these reasons, it is submitted that the claims are sufficiently enabled under 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

II. Rejection under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

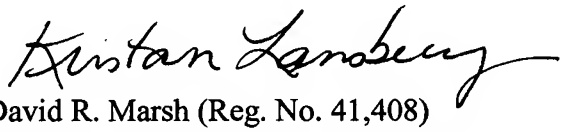
Claims 34-37 and 39-40 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Office Action at pages 6. In rejecting the claims, the Examiner asserts that the claims are indefinite for "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." *Id.* In rejecting the claims, the Examiner further asserts that Claims 34-37 "do not require any components in addition to the claim on which they depend" and "are confusing because they do not appear to further limit the subject matter of the claim on which they depend." *Id.* The Examiner further asserts that Claim 39 "does not clearly indicate what positive, active method steps are intended to be performed." *Id.*

Applicants respectfully disagree with the Examiner's rejections under 35 U.S.C. § 112, second paragraph. However, solely in order to facilitate prosecution, Applicants have amended Claims 34-37 and 39 and have canceled Claim 40 without prejudice or disclaimer as to the underlying subject matter. As such, Applicants respectfully assert that the claim rejections are rendered moot.

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-5186 should any additional information be necessary for allowance.

Respectfully submitted,



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